JMCP
JOURNAL OF MANAGED CARE PHARMACY

Methods for Insulin Delivery and Glucose Monitoring in Diabetes: Summary of a Comparative Effectiveness Review

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Supplement
August 2012
Vol. 18, No. 6
Continuing Education Activity

JMCP

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This supplement to the Journal of Managed Care Pharmacy (ISSN 1083–4087) is a publication of the Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314; 703.683.8416; 703.683.8417 (fax).

POSTMASTER: Send address changes to *JMCP*, 100 North Pitt St., Suite 400, Alexandria, VA 22314.

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Dr. Sherita Hill Golden, MD, MHS, is Associate Professor of Medicine in the Division of Endocrinology and Metabolism at the Johns Hopkins University School of Medicine, Baltimore, Maryland. She also holds joint appointments at the Welch Center for Prevention, Epidemiology, and Clinical Research and in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health in Baltimore. Dr. Golden graduated Phi Beta Kappa and summa cum laude from the University of Maryland, College Park, and Alpha Omega Alpha from the University of Virginia School of Medicine, Charlottesville, before training in internal medicine and endocrinology and metabolism at the Johns Hopkins Hospital. During her fellowship in endocrinology, she received a master of health science degree in clinical epidemiology from the Johns Hopkins University Bloomberg School of Public Health. Her primary research interest centers around identifying endocrine risk factors associated with the development of diabetes and cardiovascular disease through the incorporation of measures of hormonal function into the design of clinical trials of cardiovascular risk modification, observational studies of incident cardiovascular disease and diabetes, and studies evaluating diabetic complications. Her current research focuses on studying the neuroendocrine response to chronic psychological stress as a risk factor for diabetes and cardiovascular disease. Dr. Golden is Director of the Johns Hopkins Inpatient Diabetes Management Service and serves as Chairperson of the Glucose Management Committee for Johns Hopkins Hospital. She is also Chairperson of the Epidemiology and Biostatistics Interest Group for the American Diabetes Association and Chairperson of the Diabetes Committee for the American Heart Association's Council of Nutrition, Physical Activity, and Metabolism. She is a former Robert Wood Johnson Minority Medical Faculty Career Development Award recipient, and her current research is funded through the National Institute of Diabetes, Digestive, and Kidney Diseases. Dr. Golden has authored and co-authored over 60 original articles and book chapters in the areas of diabetes and cardiovascular disease epidemiology.

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Methods for Insulin Delivery and Glucose Monitoring in Diabetes: Summary of a Comparative Effectiveness Review

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Target Audiences

This CME activity is designed to meet the educational needs of physicians, pharmacists, nurses, and case managers involved in the management and care of patients with diabetes.

Learning Objectives

Based on the findings from the Agency for Healthcare Research and Quality's (AHRQ) comparative effectiveness review of insulin delivery and glucose-monitoring modalities for diabetes, participants should be able to:

1. Compare the benefits of insulin delivery systems in improving clinical outcomes, glycemic control, hypoglycemia, and quality of life in diabetic patients receiving intensive insulin therapy
2. Evaluate the differential effect of glucose-monitoring approaches on the process measures and intermediate and clinical outcomes in diabetic patients receiving intensive insulin therapy
3. Apply the AHRQ findings to guide effective, patient-centered clinical decisions

Funding

There is no fee for this CME/CE activity. This learning activity was prepared and funded under contract HHSA290201000006G from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services (HHS).

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DISCLOSURES

Sherita H. Golden received grant support for the original evidence report on which this article is based from the Agency for Healthcare Research and Quality. She reports no financial interest or relationships with companies with commercial interest in diabetes therapies or insulin delivery or glucose-monitoring devices. She was compensated by PRIME Education, Inc., to review the manuscript.

Tamar Sapir is an employee of PRIME Education, Inc., a medical education company that receives grants and funding for educational programs from various pharmaceutical manufacturers. Sapir analyzed the source document and wrote and revised this summary with the assistance of Golden.

Carrie McAdam Marx received compensation from PRIME Education, Inc., for writing the commentary and reports no consulting relationships related to the subject of this report.

Debbie DeMuria and Kathleen A. Jarvis report no financial interest or relationships with companies with commercial interest in diabetes therapies or insulin delivery or glucose-monitoring devices. Sherman Podolsky reports a consulting relationship with Millenium Pharmaceuticals, a company owned by Takeda Pharmaceuticals. DeMuria, Jarvis, and Podolsky were compensated by PRIME Education, Inc., to review the manuscript. Bridget M. Flavin and Melissa Butler report no financial interests or other relationships with companies with commercial interests in methods for insulin delivery and glucose monitoring or other potential conflicts of interest related to the subjects in this report.

ACKNOWLEDGEMENTS

This summary article is based on a comparative effectiveness review conducted by investigators at the Johns Hopkins University Evidence-based Practice Center, Rockville, Maryland. Dr. Golden acknowledges the authors of the Evidence Report, Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness—Drs. Todd Brown, Hsin-Chieh Yeh, Nisa Maruthur, Padmini Ranasinghe, Zackary Berger, Eric Bass, Mr. Yong Suh, and Ms. Elisabeth Haberl and Mrs. Lisa Wilson. The authors of the review acknowledge Dr. Felicia Hill-Briggs for her guidance on the quality of life synthesis, Drs. Elie Donath and Ghanshyam Palamaner Subash Shantha for their assistance with reviewing articles, and Eric Vohr for his assistance in editing the report. They also thank the Key Informants, Technical Expert Panel, Peer Reviewers, and Task Order Officer, Dr. Christine Chang.

For contributing the clinical commentary included in this *JMCP* supplement, the authors thank Carrie McAdam Marx, PhD, RPh, of the University of Utah, Pharmacotherapy Outcomes Research Center.

This learning activity was prepared and funded under contract HHSA290201000006G from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services (HHS). The activity is intended to inform health professionals about AHRQ's comparative effectiveness research findings and to identify methods for incorporating the findings into practice. The content in this article is based on the evidence that was available at the time the AHRQ comparative effectiveness review on insulin delivery and glucose-monitoring modalities for diabetes was published (July 2012; AHRQ Publication No. 57). The full report is available at: http://effectivehealthcare.ahrq.gov/ehc/products/242/749/CER57_Insulin-Delivery_FinalReport_20120703.pdf.

Methods for Insulin Delivery and Glucose Monitoring in Diabetes: Summary of a Comparative Effectiveness Review

Sherita Hill Golden, MD, MHS, and Tamar Sapir, PhD

ABSTRACT

BACKGROUND: Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia, which when untreated can lead to long-term complications, including micro- and macrovascular complications. Tight glycemic control with intensive insulin therapy has been suggested to reduce the risk of such complications in several diabetes populations; however, such an approach can also be associated with risks and challenges. There are currently several modalities available to deliver insulin and monitor glucose levels to achieve glycemic goals in diabetic patients.

In July 2012, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review on the comparative effectiveness of insulin delivery systems and glucose-monitoring modalities in diabetic patients receiving intensive insulin therapy. Studies from 44 publications included in the review compared the effects of continuous subcutaneous insulin infusion (CSII) with multiple daily injections (MDI) and/or real time-continuous glucose monitoring (rt-CGM) with self-monitoring of blood glucose (SMBG) among children, adolescents, or adults with either type 1 (T1DM) or type 2 diabetes (T2DM), or pregnant women with pre-existing diabetes (either T1DM or T2DM). This comparative effectiveness review evaluated which modality results in improved glycemic control, less hypoglycemia, better quality of life, and/or improved clinical outcomes. The numerous technologies and the challenges that clinicians face when determining which patient population may benefit from different insulin delivery systems and glucose-monitoring approaches motivated AHRQ to synthesize the available information to assist health professionals in making evidence-based practice decisions for their patients. The review also delineates advances in insulin delivery and glucose-monitoring systems, practical methods to achieve tight glycemic control and strategies to minimize associated risks, as well as highlights gaps in research and areas that need to be addressed in the future.

OBJECTIVES: To (a) educate health care professionals on the findings from AHRQ's 2012 comparative effectiveness review on insulin delivery and glucose-monitoring modalities in patients with diabetes; (b) apply review findings to make treatment decisions in clinical practice; and (c) identify shortcomings in the current research and future directions relating to the comparative effectiveness of insulin delivery and glucose-monitoring modalities for patients with diabetes.

SUMMARY: The AHRQ systematic review of randomized clinical trials reveals that both insulin delivery modalities (CSII and MDI) demonstrate similar effectiveness on glycemic control and severe hypoglycemia in children and adolescents with T1DM and in adults with T2DM. In adults with T1DM, hemoglobin A1c decreased more with CSII than with MDI with low strength of evidence, but one study heavily influenced these results. In children and adults with T1DM, the use of CSII was associated with improved quality of life compared with MDI, with low strength of evidence, while there was insufficient strength of evidence to make conclusions regarding the quality of life for adults with T2DM. The study investigators suggest that the modality to deliver intensive insulin therapy can be individualized to patient preference in order to maximize quality of life. On all measured outcomes, there was insufficient or low strength of evidence regarding pregnant women with pre-existing diabetes.

The AHRQ investigators found studies comparing the effectiveness of glucose-monitoring modalities in individuals with T1DM only. The systematic review demonstrates that rt-CGM is associated with greater lowering of A1c compared with SMBG (high strength of evidence) without affecting the risk of severe hypoglycemia (low strength of evidence) or quality of life (low strength of evidence) in nonpregnant individuals with T1DM, particularly when compliance with device use is high. Additional findings suggest that the use of sensor-augmented insulin pumps (rt-CGM + CSII) is superior to the use of MDI/SMBG use in lowering A1c in nonpregnant individuals with T1DM (moderate strength of evidence). Comparison of other outcome measures did not yield firm conclusions due to low or insufficient evidence.

J Manag Care Pharm. 2012;18(6):S3-S17

Diabetes mellitus is defined as a group of metabolic diseases marked by hyperglycemia, or high levels of blood glucose, which results from defects in insulin production and/or insulin action. When hyperglycemia remains untreated, it can lead to long-term complications including microvascular complications (e.g., nephropathy, retinopathy, and neuropathy) and macrovascular complications (e.g., coronary heart disease, peripheral arterial disease, and cerebrovascular disease).[1] According to the Centers for Disease Control and Prevention (CDC), about 8.3% of the population in the United States, including children and adults, have diabetes, and its prevalence is likely to be increased to nearly 10% by 2050.[2-4] The high prevalence rate results in an increasing proportion of the population dependent on antidiabetic therapies to achieve normoglycemia and to lower the risk of complications associated with the disease.

Type 1 diabetes mellitus (T1DM), which accounts for 5% to 10% of all diabetes cases, is an autoimmune disease characterized by the destruction of the pancreatic beta cells and insulin deficiency. Although T1DM can develop at any age, it usually occurs in children and young adults. Individuals with T1DM require daily insulin administration by injection or an insulin pump in order to survive, maintain glycemic control and normal body weight, and promote normal development in children.[1] Type 2 diabetes mellitus (T2DM) accounts for 90% to 95% of all diabetes cases in adults in the United States and results from insulin resistance as well as impaired insulin secretion by the beta cells in the pancreas. As the disease progresses and the need for insulin rises, the pancreas can eventually lose its ability to produce insulin, necessitating insulin therapy.[1] In pregnant women with pre-existing T1DM or T2DM, maternal hyperglycemia is associated with worse pregnancy outcomes and high risk of maternal, fetal, and neonatal complications such as delivery complications, fetal anomalies, macrosomia, stillbirth, and neonatal hypoglycemia, which can be minimized with intensified glycemic control.[5,6]

The use of intensive insulin therapy to achieve tight glycemic control has been shown to reduce the risk of micro- and macrovascular complications in T1DM and T2DM[7-10] and to minimize maternal, fetal, and neonatal complications in pre-existing diabetes during pregnancy.[5] However, such an approach can also be associated with risks and challenges, such as increased risk of severe or nonsevere hypoglycemia and weight gain, which can be a source of distress and anxiety and a barrier to achieving glycemic goals.[9,11,12] The role of tight glycemic control in older individuals with diabetes is less certain, and clinicians currently recommend it only for those who are functional, cognitively intact, and have a significant life expectancy.[13] Therefore, it is important for care providers and their patients to understand the importance of achieving glycemic goals and also the associated risks and barriers in order to make informed decisions as to which patients will benefit the most from intensive insulin therapy.

Approaches for Intensive Insulin Delivery

In current practice, tight glycemic control is achieved with a combination of physiological basal and mealtime (prandial) insulins that mimic normal pancreatic function (i.e., peakless basal insulin secretion, rapid release of insulin in response to meals, and rapid clearance of the prandial insulin peak). These insulin therapies can be administered to patients either as multiple daily injections (MDI) via a syringe or a pen or by external continuous subcutaneous insulin infusion (CSII) via a pump, which is intended to deliver insulin in a manner that most closely mimics the body's physiologic release of insulin. The use of CSII may improve treatment adherence, dosing accuracy, and lifestyle flexibility; however, it can also be technically demanding, costly, and requires a high level of engagement.[14] Professional organizations, such as the American Association of Clinical Endocrinologists, currently recommend CSII for patients with T1DM who are not achieving glycemic goals despite adherence to a maximal MDI regimen, especially when they have wide and erratic glycemic excursions, frequent severe hypoglycemia and/or hypoglycemia unawareness, marked dawn phenomenon, or are pregnant or planning to become pregnant.[14,15] Experts may also recommend CSII for patients with T1DM who prefer pump therapy, as it may be more suitable to their lifestyle, regardless of the level of glycemic control, and in defined select patients with T2DM (e.g., C-peptide positive with suboptimal control on maximal program of basal/bolus injections, substantial dawn phenomenon, erratic lifestyle, or severe insulin resistance).[15] In the United States, the level of insulin pump usage has been estimated at 20% to 30% in patients with T1DM and less than 1% in patients with T2DM.[15,16]

Blood Glucose-Monitoring Modalities

There are currently several modalities available to assess and monitor blood glucose levels in diabetic patients. In patients with both T1DM and T2DM, the most widely accepted modality to monitor long-term glycemic control is the measurement of glycosylated hemoglobin, specifically hemoglobin A1c (A1c), every 3 months.[17] In pregnant women with pre-existing diabetes, clinicians need to monitor weekly fasting and post-prandial glucose levels, as the instant feedback on glycemic control is important to prevent fetal and maternal complications during pregnancy.[18] Additionally, patients using multiple insulin injections or insulin pump therapy are encouraged to perform self-monitoring of blood glucose (SMBG) by fingerstick, at least 3 times daily. The results provide specific and timely feedback on glycemic levels, allowing patients and their clinicians to evaluate individual response to therapy, assess whether glycemic goals have been achieved, and make short-term adjustments in insulin therapy.[19] However, challenges associated with SMBG, such as pain, stress, cost, and behavioral and technical skills, have led to the development and approval of retrospective continuous glucose-monitoring (CGM)[20] and real-time continuous glucose-monitoring (rt-CGM)[21] devices as supplements to SMBG. The use of CGM allows clinicians to use the data retrospectively and to make adjustments to therapy, while the use of rt-CGM can provide real-time, prospective, and retrospective feedback data. Also, alarms may be set to notify patients of hyperglycemia, hypoglycemia, or rapid glucose changes, thereby enabling early interventions to prevent severe glycemic excursions.[20] Because of these advantages, physicians prefer rt-CGM to retrospective CGM in the clinical setting. Experts currently recommend rt-CGM for patients with T1DM who frequently experience hypoglycemia or hypoglycemia unawareness, have excess glycemic excursions, or are pregnant or plan to become pregnant.[20] Other available devices combine rt-CGM technology with CSII, such as sensor-augmented pumps, and technologies are continuously improving.[22] These devices are capable of detecting fluctuating blood glucose levels and trends in changing blood glucose and can adjust dosing of insulin infusion prospectively. It is also important to note that success in improving glycemic levels with any device depends on adherence to ongoing use of the device. Patients who are adherent and engaged in their insulin delivery and glucose-monitoring modalities, and effectively collaborate and communicate with their health care teams, will likely achieve the most beneficial outcomes.[23]

Comparative Effectiveness Review of Insulin Delivery and Glucose-Monitoring Modalities

Given the new modalities and technologies available for insulin delivery and glucose monitoring, clinicians face challenges in clinical practice to determine how to identify patients who will most benefit from the use of the different modalities in terms of improved glycemic, clinical, and patient-reported outcomes. Therefore, clinicians will appreciate additional data

and information that may assist their clinical decision making when considering various modes of insulin delivery and glucose monitoring for specific types of patients with diabetes to achieve desired clinical outcomes.

In June 2012, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review (CER) of various methods of insulin delivery and glucose monitoring for patients with diabetes receiving intensive insulin therapies.[24] The review, conducted by investigators at the Johns Hopkins University Evidence-Based Practice Center (EPC) in Baltimore, Maryland, analyzed whether the mode of intensive insulin therapy (CSII vs. MDI) resulted in better glycemic control, less hypoglycemia, improved quality of life, and improved clinical outcomes in children, adolescents, and adults with T1DM and T2DM and pregnant women with pre-existing T1DM or T2DM. The investigators also sought to determine whether these outcomes varied by the mode used for blood glucose monitoring (rt-CGM vs. SMBG) in the same populations.[24] This supplement provides a summary of the key questions, methods, and outcomes identified in the AHRQ's CER, as well as implications and commentary on clinical applicability of the findings that will help guide care providers to make informed decisions and improve patient outcomes.

AHRQ's Systematic Review Methods

This section summarizes the methods by which the EPC investigators conducted their comparative effectiveness review of studies on the methods for insulin delivery and glucose monitoring. Inclusion and exclusion criteria of studies analyzed in the review are summarized in Table 1. Complete details about the systematic review methods are available in the full technical report.[24]

Key Questions and Comparisons

The EPC investigators based their CER on 2 key clinical questions, which are summarized below:

Key Question 1: In patients receiving intensive insulin therapy, does the mode of delivery (CSII vs. MDI) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus?

For this key question, the investigators sought to analyze whether the effects and outcomes of the insulin delivery mode differ in diabetic populations according to diabetes status (T1DM or T2DM), age group (young children, adolescents, and adults), and pregnancy status (pre-existing T1DM or T2DM).

Key Question 2: In patients using intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (rt-CGM vs. SMBG) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus (i.e., what is the incremental benefit of rt-CGM in patients already using intensive insulin therapy)?

For this key question, the investigators sought to analyze whether the effects and outcomes of the glucose-monitoring mode differ in diabetic populations according to diabetes status (T1DM or T2DM), age group (young children, adolescents, and adults), pregnancy status (pre-existing T1DM or T2DM), and mode of intensive insulin delivery (MDI or CSII). In this key question, the EPC investigators compared the effectiveness of rt-CGM versus SMBG, as well as the effectiveness of sensor-augmented pumps (rt-CGM + CSII) versus MDI/SMBG.

Description of Outcome Measures

The process measures, intermediate outcomes, and clinical outcomes analyzed in the included studies are summarized in Table 1. For each key question, process measures assessed included ratio of basal to bolus insulin, frequency of adjusting insulin therapy, adherence to insulin therapy or sensor use, and frequency of health care visits. The primary intermediate outcome was A1c, and secondary intermediate outcomes included hyperglycemia, weight gain, and frequency of hypoglycemia. The long-term clinical outcomes included microvascular complications (nephropathy, retinopathy, and neuropathy), macrovascular complications (coronary heart disease, cerebrovascular disease, and peripheral arterial disease), severe hypoglycemia, quality of life, mortality, fetal outcomes, and maternal pregnancy outcomes (C-section rates). The assessment tools used to measure quality of life (general, disease-specific, and treatment-specific) are summarized in Table 2.

Literature Search and Study Selection

The investigators of the AHRQ review identified primary studies by searching the databases MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The review covered publications from 1994 (first year that insulin analogues were used) to July 2011, excluding studies of outdating technologies. Study selection criteria were based on applicability to the 2 key clinical questions. Inclusion and exclusion criteria for selection of studies for the review are summarized in Table 1. Out of 7,002 citations identified in the search results, 41 studies from 44 publications met inclusion criteria for this review. Listed below are the numbers and types of studies identified:

Comparative effectiveness of CSII versus MDI (28 studies)

- Children or adolescents with T1DM (9 studies)
- Adults with T1DM (9 studies)
- Adults with T2DM (4 studies, 5 publications)
- Pregnant women with pre-existing T1DM or T2DM (6 studies)

TABLE 1 Summary of Study Inclusion and Exclusion Criteria

Population and condition of interest	Inclusion • Human subjects exclusively • Studies of adults, adolescents, and children with a formal diagnosis of diabetes mellitus and pregnant women with pre-existing diabetes • Acceptable diagnoses included T1DM and T2DM. Patients with latent autoimmune diabetes of adulthood or pancreatomy were considered as T1DM. Patients with steroid-induced or transplant-induced diabetes were considered as T2DM Exclusion • Pregnant women with gestational diabetes • Patients with maturity onset diabetes of the young (MODY)
Interventions	Inclusion • Studies evaluating CSII and rt-CGM • Studies using long and rapid-acting analog and/or NPH and regular insulin in the MDI arms Exclusion • Implantable insulin pumps • Retrospective CGM devices • Use of regular insulin in the insulin pump • GlucoWatch CGM
Comparisons of interest	Inclusion • Studies that compared CSII with MDI (i.e., at least 3 injections per day) • Studies using long and rapid-acting analog and/or NPH and regular insulin in the MDI arms • Studies that compared rt-CGM with SMBG (i.e., at least 3 fingersticks per day) Exclusion • Studies of pre-mixed insulin • Studies with no concurrent comparison group
Outcomes	Inclusion of studies that evaluate 1 of the following outcomes: Process measures • Ratio of basal to bolus insulin • Frequency of adjusting insulin therapy • Adherence to insulin therapy/sensor use • Frequency of professional or allied health visits Intermediate outcomes • A1c • Hyperglycemia • Weight gain • Hypoglycemia frequency Clinical outcomes • Objective assessments of microvascular outcomes (nephropathy, retinopathy, and neuropathy) and macrovascular outcomes (coronary heart disease, cerebrovascular disease, and peripheral arterial disease) • Severe hypoglycemia • Quality of life (validated measures) • Mortality • Fetal outcomes (gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, admission to a neonatal intensive care unit) • Maternal pregnancy outcomes (Cesarean section rates)
Study type	Inclusion • RCTs and observational studies that evaluated microvascular, macrovascular, maternal, or fetal outcomes. For all other outcomes, included only RCTs • No restrictions on sample size or language Exclusion • Articles with no original data (reviews, editorials, and commentaries) or studies published in abstract form only • Case reports, case series, and cross-sectional studies • Articles published prior to 1994
Timing and setting	Exclusion • Studies in which patients used an insulin-delivery or glucose-monitoring device for less than 24 hours • Studies that were not conducted in an outpatient setting

Source: Golden SH, Brown T, Yeh H, et al. Methods for insulin delivery and glucose monitoring: comparative effectiveness. Comparative effectiveness review no. 57. July 2012.[24]

A1c = hemoglobin A1c; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; NPH = neutral protamine Hagedorn insulin; RCT = randomized controlled trial; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

TABLE 2 Quality of Life Assessment Tools Used in the AHRQ Review

Domain	Tool	Total Score Range (High Scores Indication)
General health-related QOL	Pediatric QOL Inventory	0–100 (better QOL)
	Short Form-36 (SF-36)	0–100 (higher level of health)
	Short Form-12 (SF-12)	0–100 (higher level of health)
	World Health Organization-5 Well Being Index (WHO-5)	0–100 (better well being)
Diabetes-specific QOL	Diabetes QOL	0–100 (better QOL)
	Diabetes QOL Clinical Trial Questionnaire	0–100 (higher satisfaction)
	Diabetes QOL–Youth	0–100 (better QOL)
	Problem Areas in Diabetes	0–100 (more serious problem)
Treatment-related QOL	Altered Hypoglycemia Awareness Questionnaire	0–7 (altered hypoglycemia)
	Blood Glucose Monitoring System Rating Questionnaire	0–100 (higher satisfaction)
	Diabetes Treatment Satisfaction Questionnaire	0–36 (higher satisfaction)
	Hypoglycemia Fear Survey	0–92 (higher level of fear)
	Insulin Delivery System Rating Questionnaire	0–100 (higher satisfaction)
	Phase V Outcomes system diabetes treatment satisfaction questionnaire	0–100 (higher satisfaction)
	User Acceptance Questionnaire	0–100 (more positive ratings, with exception of "problems" section)

Source: Golden SH, Brown T, Yeh H et al. Methods for insulin delivery and glucose monitoring: comparative effectiveness. Comparative effectiveness review no. 57. July 2012.[24]

AHRQ = Agency for Healthcare Research and Quality; QOL = quality of life.

Comparative effectiveness of rt-CGM versus SMGB (9 studies, 10 publications)

- Children and adults with T1DM (9 studies, 10 publications)
- No studies in patients with T2DM or among pregnant women with pre-existing T1DM or T2DM
- Comparative effectiveness of sensor-augmented pumps versus MDI and SMBG in children and adults with T1DM (4 studies, 5 publications)

Assessments of Study Quality and Strength of Evidence

To evaluate the quality of the randomized controlled trials (RCTs) included in their assessment, the EPC investigators used a dual independent review of article quality based on the Cochrane Collaboration's Risk of Bias Tool,[25] supplemented with items from AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[26] The overall quality of the individual studies was graded as *good*, *fair*, or *poor* based on the risk of bias.

- Good studies are considered to have valid results and have a low risk of bias, as evidenced by clear descriptions of their patient populations, settings, interventions, and treatment groups. Moreover, good studies are characterized by valid approaches to allocating patients to groups, low dropout rates and reporting of dropouts, and appropriate methods for preventing bias, measuring outcomes, and analyzing and reporting results.
- Fair studies are susceptible to bias, although not to a degree that invalidates the results. Fair studies may also be characterized by missing information or methodological weaknesses.
- Poor studies have significant bias that may invalidate their results. Moreover, poor studies tend to have large amounts of missing information or serious errors in design, analysis, or reporting.

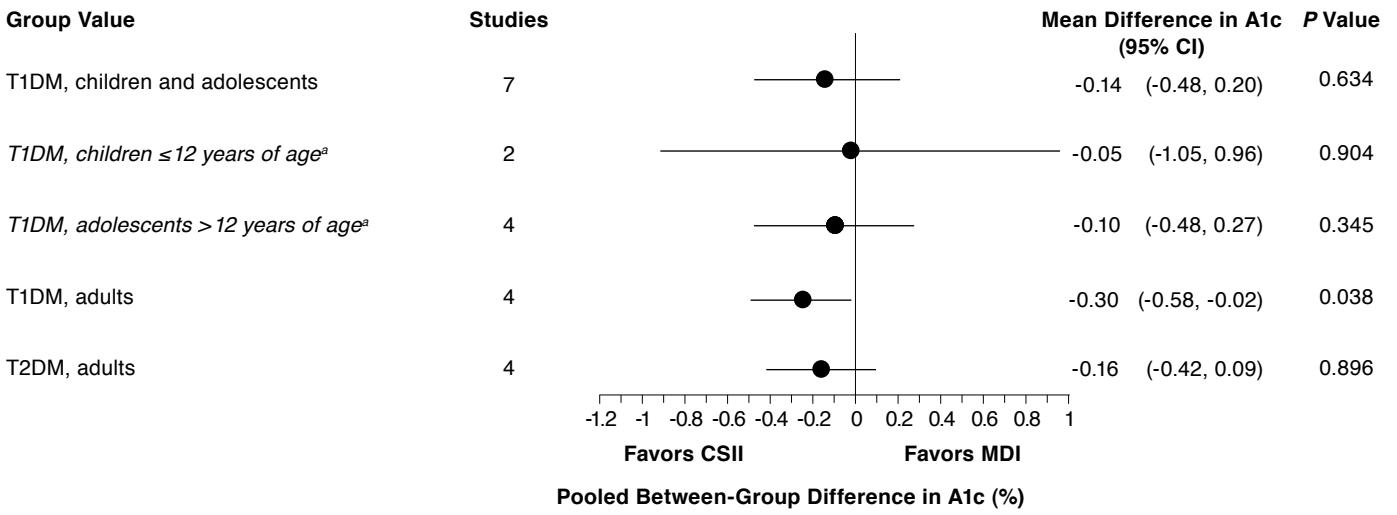
For observational studies, the investigators selected items from the Downs and Black quality checklist,[27] supplemented with items from AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[26]

At the completion of the review, the EPC investigators rated the strength of study evidence for each intervention comparison for each outcome by adapting an evidence-grading scheme recommended in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[26] This grading considers factors regarding the body of evidence such as its limitations, consistency, directness, precision, publication bias, and the magnitude of the effect. The evidence was graded as *high*, *moderate*, *low*, or *insufficient*. The first 3 of these grades indicate the investigators' confidence in the extent to which the evidence reflects true treatment effect. A grade of *insufficient* indicates that evidence either does not exist or does not permit the estimation of effect.

Comparative Effectiveness of CSII Versus MDI

The following section focuses on the AHRQ review findings in response to Key Question 1. Investigators analyzed the comparative effectiveness of CSII versus MDI in diabetic populations requiring intensive insulin therapy, including children and adolescents, adults, and pregnant women with pre-existing diabetes. The analysis focused on process measures, intermediate outcomes, and clinical outcomes, as summarized in Table 1.

FIGURE 1 Pooled Between-Group Difference in A1c Change from Baseline (%) Comparing CSII and MDI Among Children, Adolescents, and Adults with T1DM, and Adults with T2DM



Adapted from: Golden SH, Brown T, Yeh H, et al. Methods for insulin delivery and glucose monitoring: comparative effectiveness. Comparative effectiveness review no. 57. July 2012.[24]

[a]*Subanalyses were performed on children (≤12 years of age) and adolescents (>12 years of age) with T1DM. One study did not report the ages of participants and was excluded from subanalyses. Data for pregnant women with pre-existing T1DM or T2DM were not included due to lack of randomized controlled trials.*

A1c = hemoglobin A1c; CI = confidence interval; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Children and Adolescents with T1DM

Nine studies (4 parallel arm RCTs, 3 randomized cross-over trials, and 2 nonrandomized trials), of which 1 good quality, were used to evaluate CSII versus MDI therapy in children and adolescents with T1DM.[28-37] Participants generally had diabetes for 5 to 6 years prior to study entry, had poor glycemic control at study entry (mean A1c, 8% to 9%), and were treated in the intervention groups for an average of 52 weeks. The mean age of participants in the RCTs was 16.5 years (range, 4.4 to 18.9 years) and 11.4 years (range, 4.4 to 17.9 years) in the MDI and CSII groups, respectively, and 1 study did not report age of participants. Most of the studies did not the report the number of patients screened.

A meta-analysis found a mean between-group difference in A1c of -0.14% in favor of CSII; however, this difference was not statistically significant (NS; 95% confidence interval [CI], -0.48 to 0.20; $P = 0.41$). The evidence for this outcome was rated as moderate strength. Similar results were seen in A1c among adolescents over 12 years of age, while less difference was seen among children 12 years of age and younger (Figure 1). Also, no significant difference was observed between CSII and MDI in measures for daytime[29,31,36] and nocturnal hypoglycemia[35,36] (low strength of evidence), severe hypoglycemia[29] (low strength of evidence), frequency of hyperglycemia[37] (insufficient strength of evidence), and ratio of basal to bolus insulin (insufficient strength of evidence).[33] A single study that found significantly fewer episodes of mild hypoglycemia (< 70 milligrams per deciliter [mg/dL]) in the CSII group compared with the MDI group was insufficient to make a conclusion regarding the comparative effectiveness of CSII versus MDI for mild hypoglycemia.[37] No significant difference was reported in the change from baseline body mass index (BMI) standard deviation score (SDS) between the MDI and CSII intervention groups; however, scores decreased slightly more with CSII (mean between-group difference -0.12 units; 95% CI, -0.55 to 0.30; $P = 0.984$).[36,37] No significant difference was found in general quality of life between CSII and MDI in this population (mean between-group difference, 2.3; 95% CI, -6.9 to 11.5; $P = 0.95$; low strength of evidence). Of studies that reported Diabetes Quality of Life-Youth scores, 1 good-quality study showed improvement favoring CSII,[36] while another study did not find a difference in diabetes quality of life between the 2 interventions.[35] When examining diabetes treatment-related quality of life, as assessed by Diabetes Treatment Satisfaction Questionnaire (DTSQ), a meta-analysis of 2 studies favored CSII over MDI (mean between-group difference, 5.7; 95% CI, 5.0-6.4; $P < 0.001$), although the variation in the effect due to heterogeneity was significant (low strength of evidence).[29,37] The investigators of the review did not find any studies addressing certain process measures (frequency of adjusting

insulin therapy, adherence, health visits) and clinical outcomes (microvascular and macrovascular disease and mortality) in this patient population.[24]

The investigators were not able to perform meta-analyses for the outcome measures of nonsevere hypoglycemia, weight gain, and quality of life measures due to the limited study number and heterogeneity in assessments, which resulted in low strength of evidence for these outcomes. There was insufficient strength of evidence to draw conclusions for hyperglycemia and ratio of basal to bolus insulin in children and adolescents with T1DM.

Adults with T1DM

Nine studies (8 RCTs and 1 nonrandomized trial), including 21 to 272 participants, evaluated the effectiveness and safety of CSII versus MDI among adults with T1DM.[38-46] There were no studies identified that focused solely on an elderly population with T1DM, and studies did not report on race and many items of interest to determine the applicability of the studies to all adults with T1DM. The mean duration of T1DM ranged from 14.4 to 25 years in the study participants,[38-41,43-46] and the duration of interventions ranged from 5 weeks to 1 year.[38-46] Intervention arm-specific A1c ranged from 7.4% to 9.3% at baseline.[38,39,41,44,45] Eligibility criteria for MDI and CSII varied significantly across studies, and more than half of the studies did not report on who withdrew from the studies.

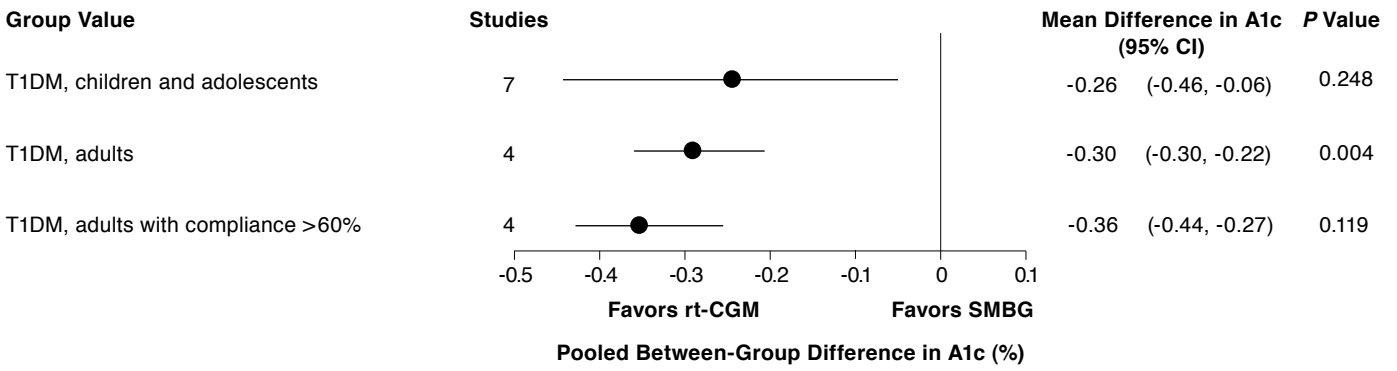
A meta-analysis of 4 RCTs, including 2 good quality studies, found that CSII decreased A1c from baseline more than MDI (combined mean between-group difference, -0.30%; 95% CI, -0.58 to -0.02; $P = 0.038$; Figure 1; low strength of evidence).[38,40,44,45] However, the pooled estimate was influenced by 1 study[44] in which participants had a higher A1c at enrollment (9.3% vs. 7.7% to 8.2%),[38,45] resulting in greater opportunity for a large decrease in A1c in that study (-0.84%) compared with other studies (-0.1% to 0.25%). After removal of this study from meta-analysis, the difference in A1c levels between intervention groups was no longer detectable. Evaluation of hypoglycemia measures in adults with T1DM revealed a significant increase in the incidence of symptomatic hypoglycemia events per person-year with CSII compared with MDI (combined incidence rate ratio, 1.30; 95% CI, 1.18-1.42; $P < 0.001$); although there was significant statistical heterogeneity in this meta-analysis (low strength of evidence).[38,40,45] One study reported more symptomatic and asymptomatic hypoglycemia between 8 a.m. and midnight in the MDI intervention arm ($P < 0.05$; low strength of evidence).[49] Three RCTs included analyses of nocturnal hypoglycemia; 2 had similar proportions of episodes in both intervention arms;[38,39] and 1 study reported fewer episodes per person in the CSII compared with the MDI group[42] (low strength of evidence). Based on a meta-analysis, there was no difference seen in severe hypoglycemia incidences between the 2 intervention groups (low strength of evidence).[39,41,42,46] The mean between-group difference in fasting glucose over 6 months was -12.3 mg/dL (95% CI, -32.9 to 8.2; P = NS) favoring CSII in 1 study,[38] while 2 other studies reported no difference in fasting glucose between the intervention groups (low strength of evidence).[43,44] Additionally, the mean between-group difference in pre-prandial glucose over 6 months was -17.1 mg/dL (95% CI, -42.1 to 8.0; P = NS) favoring CSII in 1 study,[38] and in another study, pre-dinner glucose was lower with CSII (128 mg/dL) compared with MDI (148 mg/dL) at the end of 5 weeks (P = NS).[42] Studies that measured post-prandial glucose reported slightly lower post-prandial glucose with CSII compared with MDI treatment (low strength of evidence).[38,42] There was insufficient strength of evidence to determine the relative effects of CSII and MDI on glucose at bedtime.[44] Analysis of weight gain among the intervention groups saw no significant difference between CSII and MDI (low strength of evidence).[39,40,43,44] Two studies found improvement in general quality of life[41] that favored CSII; a meta-analysis of 4 studies using the Diabetes Quality of Life questionnaire also favored CSII for diabetes-specific quality of life[40] (low strength of evidence). There was insufficient strength of evidence to conclude a difference in diabetes treatment-related quality of life between interventions, as participants scored similarly on the Altered Hypoglycemia Awareness Questionnaire and Hypoglycemia Fear Survey in 1 study.[40] The investigators found no studies evaluating the effects of MDI versus CSII among adults with T1DM in terms of process measures (ratio of basal to bolus insulin, frequency of adjusting insulin therapy, adherence, and health visits), or clinical outcomes (microvascular and macrovascular disease and mortality).

Adults with T2DM

Four RCTs (3 parallell-arm randomized trials, and 1 randomized cross-over trial) evaluated the effects of CSII and MDI in terms of mortality, A1c, hypoglycemia, severe hypoglycemia, hyperglycemia, weight, and quality of life in adults with T2DM.[47-50] Number of participants ranged from 20 to 66 adults per arm in the included studies. Only 1 study included participants 60 years of age or older.[49] Duration of intervention was at least 18 weeks in the included studies.

The results of a meta-analysis including all 4 studies suggests there is no difference between CSII and MDI effect on A1c (mean between-group difference from baseline, -0.16%; 95% CI, -0.42 to 0.09; $P = 0.21$; Figure 1; moderate strength of evidence).[48-50] Additionally, the evaluation of hypoglycemia revealed no difference between CSII and MDI in mild hypoglycemia (moderate strength of evidence; combined relative risk [RR] = 0.90; 95% CI, 0.78-1.03; $P = 0.129$) or severe hypoglycemia (low strength of evidence; RR = 0.76; 95% CI, 0.26-2.19; $P = 0.61$).[47,49] In a single study, nocturnal hypoglycemia was less common in the CSII arm compared with the MDI arm (insufficient strength of evidence).[47] The strength of evidence

FIGURE 2 Pooled Between-Group Difference in A1c Change from Baseline (%) Comparing rt-CGM and SMBG Among Children, Adolescents, and Adults with T1DM



Adapted from: Golden SH, Brown T, Yeh H, et al. Methods for insulin delivery and glucose monitoring: comparative effectiveness. Comparative effectiveness review no. 57. July 2012.[24]

A1c = hemoglobin A1c; CI = confidence interval; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus.

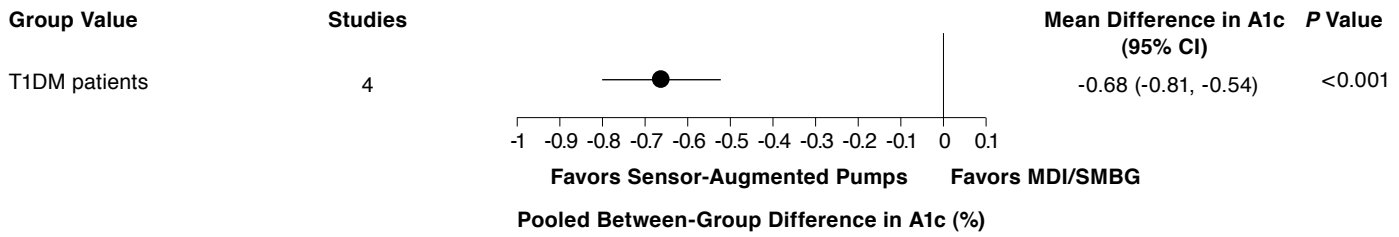
was low comparing CSII with MDI for hyperglycemia based on 2 studies. One study reported quantitative results, showing a difference in mean post-prandial glucose at 24 weeks: 167 mg/dL in the CSII group and 192 mg/dL in the MDI group (mean between-group difference, -25 mg/dL; 95% CI, -45 to -5; $P = 0.019$). However, at the end of the study, glucose measurements from other time points were similar between intervention groups. The incidence of blood glucose over 350 mg/dL was higher in the MDI arm compared with the CSII arm (26 events vs. 6 events), affecting 18% of participants in the MDI arm versus 5% in the CSII arm (RR = 0.28; 95% CI, 0.08-0.94).[47] The investigators found only 1 study comparing the relative effects of CSII and MDI on mortality, reporting 1 death due to cancer in the CSII treatment arm.[49] The study reported no further information on this event and did not include the occurrence of events in the MDI arm. Two studies found no significant effect of treatments on weight gain (low strength of evidence). The strength of evidence was graded as insufficient for general, diabetes-specific, and diabetes treatment-related quality of life. A single study showed no difference in general quality of life and diabetes-specific quality of life,[49] while another study showed improvement in diabetes treatment satisfaction favoring CSII.[47] The investigators found insufficient strength of evidence evaluating the effects of MDI versus CSII among patients with T2DM in terms of any of the process measures and microvascular or macrovascular disease, as no studies were found on these outcomes.

Pregnant Women with Pre-Existing T1DM

Six observational studies (2 prospective studies and 4 retrospective studies) evaluated the effects of CSII versus MDI therapy in pregnant women with T1DM and reported on maternal and fetal outcomes.[51-56] The mean age of study participants was 26 to 31 years, with most participants in the CSII group enrolled into the studies prior to becoming pregnant. Most participants had diabetes duration of 7.7 to 13.9 years, with participants in the CSII groups having the longest duration of diabetes. All studies were conducted in European countries, and studies contained limited descriptions of study methodology, study populations, intervention, and outcomes.

The results of all 6 studies suggest improvement in A1c in both the CSII and MDI groups during pregnancy without any significant difference between the intervention groups during any of the trimesters (low strength of evidence).[51-56] The strength of evidence of the data that compared CSII with MDI among pregnant women with pre-existing T1DM was insufficient for all other maternal and neonatal outcomes due to lack of RCTs and, therefore, a high risk of bias. There was no statistical difference in maternal weight gain,[52,54,56] gestational age at delivery,[51,53-55] birth weight,[53-55] and minor congenital anomalies[51,54] between the CSII and MDI intervention groups. Also, meta-analyses of retrospective studies showed nonsignificant relative risks for rates of C-section (RR = 1.01; 95% CI, 0.86-1.20),[53-56] severe hypoglycemia (RR = 0.78; 95% CI, 0.23-2.65),[54-56] admission to the neonatal intensive care unit (RR = 0.84; 95% CI, 0.43-1.68),[54,55] pre-term delivery (RR = 0.98; 95% CI, 0.67-1.43),[53-56] and frequency of neonatal hypoglycemia (RR = 1.01; 95% CI, 0.86-1.20).[53-56] Additionally, meta-analyses for major congenital anomalies showed a pooled RR of 2.12 that favored MDI but was not statistically significant.[55,56] Due to the lack of RCTs, which leads to a high risk of bias of all the above outcomes, the EPC investigators suggested that results were inconclusive. There was also insufficient strength of evidence for findings that showed no significant difference

FIGURE 3 Pooled Between-Group Difference in A1c Change from Baseline (%) Comparing Sensor-Augmented Pumps Versus MDI/SMBG Among Patients with T1DM



Adapted from: Golden SH, Brown T, Yeh H, et al. Methods for insulin delivery and glucose monitoring: comparative effectiveness. Comparative effectiveness review no. 57. July 2012.[24]

A1c = hemoglobin A1c; CI = confidence interval; MDI = multiple daily injections; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus.

regarding stillbirth (1 study) and neonatal (3 studies) and perinatal mortality (2 studies) rates.[51-53,56] The investigators did not find any studies in pregnant women with T1DM that evaluated maternal mortality, microvascular or macrovascular disease, quality of life, any of the process measures, or birth trauma, and no studies were identified that compared the effectiveness of CSII and MDI in pregnant women with pre-existing T2DM.

Comparative Effectiveness of rt-CGM Versus SMBG

The following section focuses on the AHRQ review findings in response to key question 2, which analyzed the comparative effectiveness of rt-CGM versus SMBG. All studies addressing this key question were conducted in children, adolescents, and adults with T1DM. The investigators did not identify studies for the comparative effectiveness of rt-CGM and SMBG in patients with T2DM or in pregnant women with pre-existing diabetes (insufficient strength of evidence).

Nine RCT studies (8 parallel-arm trials and 1 randomized cross-over trial), from good to fair quality, evaluated rt-CGM versus SMBG in children and adults with T1DM.[23,57-65] The median follow-up time for all studies was 24 weeks, and median enrollment of 132 patients was reported in 6 studies. The mean age of participants was 24 years in the rt-CGM group and 25 years in the SMBG group, with mean baseline A1c of 8.3% in both groups. The studies were conducted in diverse countries.

A meta-analysis of 7 RCTs of at least 12 weeks duration found a significant reduction in A1c with rt-CGM compared with SMBG (high strength of evidence; combined mean between-group difference, -0.3%; 95% CI, -0.37 to -0.22; $P<0.001$; Figure 2).[23,57-64] A second meta-analysis of 4 studies in children and adolescents age 18 years or younger also found a significant combined mean between-group difference in A1c from baseline in favor of rt-CGM (-0.26%; 95% CI, -0.46 to -0.06; $P=0.248$; Figure 2). The difference was confirmed by a sensitivity subset analysis that demonstrated even greater A1c reductions when only studies with more than 60% compliance rate in device use were included (-0.36%; 95% CI, -0.44 to -0.27; $P=0.119$; Figure 2). A meta-analysis of 4 RCTs indicated a significant reduction in time spent in hyperglycemic range (defined as glucose level greater than 180 mg/dL) with a mean between-group difference of -68.56 minutes/day favoring rt-CGM (moderate strength of evidence; 95% CI, -101.17 to -35.96; $P=0.326$).[23,59,61,64] There was no difference seen between the 2 intervention arms in time spent in hypoglycemic range (defined as glucose level less than 70 mg/dL) based on a meta-analysis of 4 studies (moderate strength of evidence).[23,59,61,64] Results from 2 of these trials suggested no difference in the rates of severe hypoglycemia between the rt-CGM and SMBG groups (low strength of evidence; pooled RR, 0.95; 95% CI, 0.53-1.69; $P=0.86$).[23,58-64] The investigators identified 2 studies that measured ratio of basal to bolus insulin, and the results were inconsistent. One study showed a higher percentage of basal insulin in the rt-CGM arm,[58] while another study reported higher bolus insulin percentage in the rt-CGM arm when compared with SMBG (low strength of evidence).[59] One study that measured general quality of life found no difference in parental satisfaction between the intervention arms at 12 months.[58] Another study reported improvement on the Physical Component Score of the Short Form-12 favoring rt-CGM, but no difference was seen between the comparison arms on the Mental Component Score at 26 weeks (low strength of evidence).[65] No difference was found in the effects on diabetes-related quality of life in either of 2 studies comparing rt-CGM and SMBG (low strength of evidence),[57,65] while 1 study that reported effect on quality of life related to diabetes treatment demonstrated less fear of hypoglycemia with rt-CGM than with SMBG (insufficient strength of evidence).[65] None of the studies evaluated the comparative effectiveness of rt-CGM versus SMBG in terms of mortality, microvascular or macrovascular disease, weight, or any other process measure.

Comparative Effectiveness of Sensor-Augmented Pumps Versus MDI/SMBG

Four RCTs, including 2 good quality studies, evaluated the effects of sensor-augmented pumps (rt-CGM + CSII) versus MDI/SMBG in children and adults with T1DM.[66-69] All studies provided training and used the MM Paradigm REALTime system; however, the frequency and intensity of follow-up visits differed between studies.[66-69] The mean baseline A1c in all studies was 8.6%, and participants were treated in the intervention groups for 15 weeks to 1 year.

The investigators of the study reported results from a meta-analysis of all 4 RCTs showing a significant difference in the reduction from baseline A1c that favored the sensor-augmented pump group compared with the MDI/SMBG group (moderate strength of evidence; combined mean between-group difference, -0.68%; 95% CI, -0.81 to -0.54; $P < 0.001$; Figure 3).[66-69] In addition, the review found that patients who used the sensor-augmented pumps spent significantly less time with hyperglycemia than patients with MDI/SMBG based on 2 of the 4 trials ($P < 0.001$; moderate strength of evidence).[66] However, the incidence of severe hypoglycemia and time spent in nonsevere hypoglycemia did not differ between the 2 intervention groups (moderate strength of evidence).[66,69] There was also no significant difference seen in weight gain between the intervention groups (low strength of evidence).[66,67] In terms of diabetes treatment-related quality of life, greater user acceptance, overall treatment satisfaction, and higher scores on the Blood Glucose Monitoring System Rating Questionnaire were reported with the sensor-augmented pump arm compared with the MDI/SMBG arm.[67] None of the studies identified reported on mortality, microvascular or macrovascular disease, or any of the process measures.

Study and Review Limitations

The EPC investigators noted several important weaknesses in the studies included in the CER. The majority of the RCTs comparing the effects of modalities used for insulin delivery and glucose monitoring were small, of fair to poor quality, and did not report most quality items of interest. All of the studies included in the review were efficacy studies (whether an intervention can produce a narrowly defined effect in research setting) rather than effectiveness studies. Most studies did not report on race and ethnicity, and for those that did, the majority of participants were Caucasian. The investigators were unable to draw conclusions on the effectiveness of insulin delivery and glucose-monitoring modes in children younger than 12 years, adults older than 65 years, or pregnant women with pre-existing T2DM, since only a few studies included these subpopulations. The investigators were also not able to combine data to determine effect estimates for several intermediate outcomes as they found variability and heterogeneity in the definitions and classifications of nonsevere and severe hypoglycemia, hyperglycemia, and weight gain among the studies. Even though the review included only studies of current methods used for intensive insulin therapy, heterogeneity was also found in the insulin regimens used in the MDI arms in studies comparing CSII and MDI, and there was inadequate power to stratify by the MDI insulin regimen. The studies were also heterogeneous in the assessment and reporting of quality of life outcomes, which therefore limited the quantification of the comparative effectiveness on quality of life. Additionally, no studies were identified that measured the comparative effectiveness on microvascular and macrovascular complications, which are associated with long-term diabetes. This was attributed to the fact that the longest follow-up in the studies included in the review was 52 weeks, and in order to detect long-term diabetes-related complications, a very large RCT of several years duration would be required. Another limitation in the literature was that most of the studies did not report treatment adherence to the modality used, except for the studies evaluating rt-CGM. High baseline A1c values may indicate poor adherence to previous treatment regimens, which may have biased results.

Additionally, the investigators acknowledge that all studies of rt-CGM are subject to ascertainment bias because rt-CGM, as opposed to SMBG alone, provides more data on hyperglycemia and hypoglycemia in the patients using the device. Also, studies measuring quality of life could have been subject to reporting bias because it is not feasible to perform blinded RCTs comparing the modalities for insulin delivery and/or glucose monitoring in the study participants.

As meta-analyses in general are subject to bias based on article selection criteria, multiple comparisons, and the state of the available literature, the EPC investigators could not exclude the possibility that publication bias affected their findings for each of the comparisons, although their search strategy was comprehensive and included publications in all languages.

The investigators also highlight the fact that data discussed in the CER are not generalizable to nonspecialty settings or to all patients with diabetes mellitus, since the studies excluded individuals with certain comorbidities, and the initiation, instruction, monitoring, and therapeutic changes for CSII and rt-CGM modalities are often limited to specialized settings and highly motivated patients and families.

Future Research Directions

The EPC investigators call for future research that directly addresses the gaps and methodological shortcomings associated with study designs for insulin delivery and glucose-monitoring approaches for patients with diabetes. Their recommendations highlight the need for well-conducted RCTs of intensive insulin therapy delivery and glucose-monitoring approaches focusing on young children with T1DM, pregnant women with pre-existing diabetes, and particularly in elderly

patients with diabetes who are at higher risk for adverse events associated with intensive insulin therapy.

Given the increased prevalence of T2DM in the general population, it is likely that the number of individuals with T2DM requiring insulin therapy will also rise in the years to come. Therefore, the investigators note the importance of determining which approach will be most effective for insulin delivery and glucose monitoring in patients with T2DM and recommend future studies that focus on this population. The investigators recommend that such studies should include ethnically diverse populations as T2DM is more common in nonwhites,[2] and minority individuals are at higher risk for adverse outcomes. Such studies may help guide clinical decision when considering which intensive insulin delivery and glucose monitoring may benefit specific patient populations.

Finally, the EPC investigators have urged the use of widely accepted uniform definitions of glycemic outcomes in future RCTs, as well as an agreed-upon set of quality of life measures, to allow comparisons across trials. They have also highlighted the importance of incorporating measures of adherence to treatment and suggested to possibly incorporate measures for sensor compliance as a marker for overall treatment adherence. The investigators also recommended future well-designed prospective, observational studies to determine the comparative effectiveness of insulin delivery and glucose-monitoring modalities on long-term microvascular and macrovascular complications associated with diabetes.

Conclusions

The CER, as reported by Golden et al. (2012)[24] systematically compiled the current state of evidence on the efficacy of the modalities used in clinical practice for intensive insulin delivery and glucose monitoring, in terms of diabetes-related process measures, intermediate outcomes, and clinical outcomes in children, adolescents, adults, and pregnant individuals with T1DM and T2DM.

Key Question 1

For the comparison between the insulin delivery approaches, the investigators included in their review only RCTs that used rapid-acting insulin analogs in the CSII arms and at least 3 daily injections in the MDI arms, as opposed to prior meta-analyses that used mixed modes of insulin therapies in their studies.[70,71] The systematic review demonstrated that the modes for delivering intensive insulin via CSII or MDI did not differ in terms of their effects on reduction in A1c in children and adolescents or pregnant women with T1DM, or for adults with T2DM; however, data suggested CSII achieved lower A1c in adults with T1DM (Figure 1). There was also no difference found between the 2 interventions in terms of rate of severe hypoglycemia in nonpregnant T1DM patients or adults with T2DM. The evidence was insufficient to draw conclusions regarding rates of severe hypoglycemia in pregnant women with T1DM. The studies suggest that CSII improved general and diabetes-specific quality of life, when compared with MDI in nonpregnant individuals with T1DM. The evidence was insufficient for pregnant women with T1DM and adults with T2DM. Observational studies showed, with a high risk of bias, no difference in gestational age at delivery between the 2 intervention groups; however, there was insufficient evidence to draw conclusions regarding any other maternal and fetal outcomes in pregnant women with pre-existing T1DM.

Key Question 2

The EPC investigators were only able to draw conclusions for comparison of glucose-monitoring approaches in nonpregnant individuals with T1DM receiving intensive insulin therapy, since no comparative effectiveness studies were found in adults with T2DM or pregnant women with pre-exisitng diabetes. The systematic review revealed that T1DM patients using the rt-CGM achieved lower A1c than patients in the SMBG group. Moreover, the effect was even greater in patients who were compliant with their devices. The review has also suggested that the use of rt-CGM is associated with improved A1c in children younger than 18 years old (Figure 2). These findings support recent clinical practice guidelines recommending the use of rt-CGM in children and adolescents over the age of 8 years.[72] The 2 glucose-monitoring approaches did not differ in rates of severe hypoglycemia; however, there was a significant reduction in the time spent in the hyperglycemic range favoring the rt-CGM group. In addition, although the few studies that evaluated quality of life found no difference in general and diabetes-specific quality of life between the 2 intervention groups, 1 study showed less fear of hypoglycemia with rt-CGM than with SMBG.[65] The investigators note that this has important clinical implications, as patient anxiety can be a barrier to achieving treatment goals in patients receiving intensive insulin therapy.

Finally, the EPC investigators performed a meta-analysis of RCTs comparing the use of sensor-augmented pumps (rt-CGM/CSII) with MDI/SMBG (Figure 3). The findings revealed clinically and statistically significant reductions in A1c (-0.61%), favoring sensor-augmented pumps in nonpregnant individuals with T1DM; however, the evidence was insufficient for other outcomes assessed. No other meta-analysis of this comparison was identified.

Implications for Clinical Applications

The findings from the CER indicated that both intensive insulin delivery approaches (CSII and MDI) using current rapid-acting insulin analogs demonstrate similar effectiveness in reducing A1c in adolescents and pregnant women with T1DM, and similar rates of severe hypoglycemia in nonpregnant individuals with T1DM. In adults with T1DM, CSII demonstrated

to be superior to MDI, although this was heavily influenced by 1 study. However, in terms of treatment satisfaction and quality of life, adolescents and adults with T1DM treated with CSII reported higher overall quality of life compared with patients treated with MDI; thus, the investigators implied that the clinical application of intensive insulin delivery approaches might be individualized to meet the patient's needs and preferences to optimize quality of life and treatment satisfaction.

An additional implication to clinical practice was related to the findings that rt-CGM is superior to SMBG in lowering A1c in nonpregnant T1DM patients, without affecting risk of hypoglycemia. These findings were even more pronounced in patients who were compliant with their glucose-monitoring devices. The addition of rt-CGM to CSII is more effective than MDI/SMBG in lowering A1c; therefore, the addition of this monitoring method to SMBG and intensive insulin therapy can assist in achieving glycemic targets in nonpregnant individuals with T1DM.

Commentary: Managed Care Pharmacy Perspective in Evaluating Current Modes for Insulin Delivery and Glucose Monitoring in Patients with Diabetes

With 25 million individuals (8.3% of the population) in the United States having diabetes at an annual cost of $174 billion, diabetes is a significant concern for managed care organizations.[2] Effective blood glucose management is critical for avoiding diabetes-related complications, and it has been estimated that a 1% improvement in hemoglobin A1c can reduce annual costs by as much as $950 per patient with diabetes.[73] In addition to diabetes being a progressive disease, individual patients differ in the frequency and severity of glycemic excursions, hypoglycemia susceptibility and awareness, and ability or willingness to self-manage their disease. As such, many patients with diabetes fail to maintain glycemic control.

Insulin therapy is an important therapeutic asset in managing diabetes. However, hypoglycemia is a relatively common, sometimes costly, and possibly fatal adverse event associated with insulin therapy. Thus, routine blood glucose monitoring is an important component of insulin therapy to help patients achieve desired blood glucose levels and to optimize outcomes. Given these treatment challenges, continuous subcutaneous insulin infusion (CSII) and real-time continuous glucose monitoring (rt-CGM) have been proposed as technological advances to help patients manage insulin dosing and monitor blood glucose levels to optimize glycemic control.

This current review was designed to assist decision makers regarding the comparative advantages of CSII and rt-CGM relative to multiple daily insulin injections (MDI) and self-monitoring of blood glucose (SMBG). With the possible exception of adults with type 1 diabetes (T1DM), it did not find solid evidence that CSII improves glycemic control or that it reduces nocturnal or severe hypoglycemic events relative to MDI in children and adolescents with T1DM or patients with type 2 diabetes (T2DM). However, an improvement in diabetes-specific quality of life was identified in youth and adults with T1DM. When considering the effectiveness of rt-CGM versus SMBG in patients with T1DM, glycemic control effects favored rt-CGM when compliance with rt-CGM was 60% or better. No difference in rates of severe hypoglycemia or in diabetes-related quality of life was observed. It is important to note that significant gaps in data exist for these technologies, particularly for the subgroup of insulin-treated patients who experience glycemic excursions and/or have frequent hypoglycemia and who may have the most to benefit from CSII and rt-CGM.

Given the difficulty managing a population of patients with diabetes and the consequences of poor glycemic control and hypoglycemia, providing coverage of CSII and rt-CGM is a pragmatic decision. While CSII and rt-CGM increase treatment costs, significant coverage limitations may not be warranted in certain diabetic subgroups of diabetic patients. However, managed care organizations should consider ongoing utilization and outcomes assessment to ensure that these technologies are targeted to patients most likely to benefit from these modalities.

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